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THE METABOLISM OF LEAD IN MAN IN HEALTH AND DISEASE

by

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LECTURE 2 (Part 1)

THE METABOLISM OF LEAD UNDER ABNORMAL CONDITIONS

In the Chair: R. F. GUYMER, T.D., M.A., M.D., F.R.C.S.
(Deputy-Chairman of the Executive Committee of the Council)

The normal metabolism of lead, as visualized in the terms of the preceding lecture, is a remarkably stable and uniform process. Before proceeding to the examination of the "abnormal" metabolism of lead, it is necessary to define the meaning of this term, according to our usage, and to establish the intent and scope of the presentation which is to follow. There can be little doubt that the behaviour of lead in man is affected by certain types of disease. Such effects, however, have been explored but little, and mention will be made of them only in passing. We must also omit a full discussion of therapeutic procedures designed to "mobilize" lead from the body, in favour of a brief statement of certain facts. The distribution of lead in the tissues and the rate of the excretion of lead from the body can be modified considerably by the administration of chelating agents such as British-Anti-Lewisite, derivatives of ethylenediaminetetra-acetic acid, and certain other similar compounds. The induction of specific metabolic disturbances such as those occasioned by gross increases and decreases in intake of calcium and phosphorus, or those involving drastic changes in the acid-base equilibrium of the body, exert little or no effect upon the rate of excretion of lead or on the concentration of lead in the blood; such minor changes in the metabolism of lead as are seen in association with these procedures are no greater or more prolonged than those occasioned by the accompanying changes in the throughput or temporary increases in output (diuresis) of water.

Abnormal lead metabolism, as defined for present purposes, is characterized by *quantitative* changes which result from abnormal, that is to say, unusual, conditions of exposure, as these are induced by a wide variety of industrial operations, and also by conditions which occur from time to time in the environment of the home or elsewhere. The emphasis upon the quantitative aspects of the matter derives from the fact that the *pattern* of the metabolism of lead, as we now know it is modified but slightly, and often not at all, by gross increases in the severity of exposure, or in the rate of absorption. This is not to say that there is not some subtle change in the behaviour of the lead in the tissues, or some intrinsic change in the susceptibility of the tissues to the presence of lead, whereby intoxication ensues. The nature of any such mechanism is unknown, but it is clear that its activation depends upon the presence of an adequate concentration of lead in the tissues (presumably at the right point or in the proper state). Thus to all present appearances, the metabolic process associated with saturnine intoxication differs only *quantitatively* from the normal process.

When the rate of the absorption of lead is increased beyond the range described in our somewhat arbitrary terms as "normal," there is a prompt change in the rate of the excretion of lead. This is seen first in an increase in the output of lead in the urine (provided there is no impairment of the renal secretory apparatus). It is associated with an increase in the lead content of the body, as demonstrated a little later in the intact organism by an elevation of the lead content of the blood. If the increase in the rate of absorption is maintained at a sufficient level and with sufficient uniformity over an appropriate period of time, there will be a *progressive* increase in the rate of the urinary excretion of lead, in the lead content of the body, and as an indication of the latter, in the concentration of lead in the blood.

1. THE INGESTION OF LEAD REGULARLY

General Experimental Procedures

The foregoing are illustrated by the results of a series of balance experiments, in which each of a series of young, healthy, human subjects has taken an aqueous solution of a lead salt in a known quantity with each meal on every successive day over a period of months or years.

Briefly to describe the experimental procedure, intelligent and reliable subjects were selected, after a comprehensive investigation of their previous and current personal, physiological, and medical status. In a preliminary series of observations, each subject was instructed in the collection of duplicate quantities of everything eaten and drunk, including medicines of any type taken at any time (only with the knowledge and on the advice of the supervisory physician), and food or beverages taken between meals; he was instructed further in the techniques of collecting all urine and feces, both under the ordinary conditions of daily life and in the course of the incidental illnesses of a minor type that commonly interrupt or modify the daily routines of otherwise healthy persons. Various clinical observations were made and recorded weekly (and at other necessary times), at which time duplicate samples of blood were obtained by venipuncture for analysis. A diary listing the food and beverages consumed, and recounting briefly the routine and any unusual activities of the day, was kept for the private information of the principal investigator.

At some point in this experimental regimen, after the characteristics of the normal metabolism of lead had been established, the experimental ingestion of lead was initiated by providing the subject weekly with 21 small containers, in which the desired quantity of a lead salt in aqueous solution had been measured out, so as to facilitate the ingestion of the correct dose with each meal.

Further details of procedures, which have been perfected by experience, need not be elaborated at this time, except to say that every effort was made to eliminate fortuitous and especially systematic errors in the performance of the subject and in the handling of the analytical work. No doubt, errors of sampling, especially those concerned with duplication of the food consumed, occurred from time to time, but there is little reason to doubt that those of positive and negative sign have tended to cancel each other during the prolonged periods of observation. Likewise analytical errors were inevitable, but constant checking of the analytical precision in several ways gave reasonable assurance that these would not be cumulative or systematic, and that errors of positive and negative sign would occur with approximately equivalent frequency.

In the first of such experiments after brief examination of the normal metabolic pattern, one milligram of lead was ingested daily by Subject M.R. (in addition to that which occurred in his food and beverages), over a period of 1,456 days (because of certain fortuitous omissions, the total quantity of lead administered in this way was

1,445 milligrams. The observations were carried out for an additional 250 days after the experimental ingestion of lead had been terminated, at which time the experiment was concluded at the wish of the subject.

Over the period of eight years, additional experiments of this type were conducted, in which comparable information was obtained as to the responses of three other experimental subjects to the daily ingestion of 2, 3, and 0.3 milligrams of lead respectively, as aqueous solutions taken with the meals. (Earlier experiments of this general type were carried out prior to the development of the analytical methods now in use in the Laboratory. The results, while similar, are not strictly comparable, quantitatively.) None of these was so prolonged as the first, each having been designed, primarily, around a question that could be answered in a shorter period of time. Moreover, the patience and endurance of even the most imperturbable and compliant human subject has limits. It is neither possible nor necessary to speak of the many details of these experiments at this time, nor to deal with the many experimental findings which have been or are to be presented elsewhere. Instead, certain portions of the data have been assembled in tabular form or arranged graphically, in

Table 17

Lead Intake and Output in a Healthy Human Subject (M.R.)

Successive Periods of 28 Days		Lead Ingested Milligrams	Lead Eliminated—Milligrams		
			Total	In Feces	In Urine
Control Period	1	7·26	10·57	9·92	0·65
Test Period—					
1 mg. of lead as lead acetate or lead chloride in solution, taken daily in doses of 0·333 mg. each with meals	1	36·62	29·05	28·16	0·89
	2	37·97	30·41	29·21	1·20
	3	37·79	38·69	37·62	1·07
	4	37·66	32·63	30·95	1·68
	5	42·76	34·75	32·97	1·78
	6	38·67	38·07	36·32	1·75
	7	35·74	33·12	31·81	1·31
	8	35·62	33·15	31·43	1·72
	9	35·59	35·86	35·55	2·33
	10	42·81	39·55	37·78	1·77
	11	38·43	34·81	31·74	2·07
	12	36·19	36·58	33·97	2·61

illustration of facts which are pertinent. The first of this series of experiments is presented fairly fully, in order to demonstrate the method of assembling the data for study, after which corresponding parts of others of the series are shown for comparative purposes.

Experimental Results

In Table 17, the early findings of the experiment in which subject M.R. was under observation for a little less than five years, are arranged to show the lead content of the food and beverages, and that of the feces and urine, as these have been composited for each of a series of 28-day periods (originally tabulated daily, summed up for each week, and then for each period of four weeks). The primary purpose of this table is to present the summarized findings of the initial period before the administration of lead in solution, in juxtaposition to the early months of the experimental ingestion. Only two points in the assembled data call for special notice, namely, the general trend toward a progressive increase in the urinary lead output as the experiment continued, and the lack of such increase in the fecal lead output. Both of these phenomena will appear more strikingly later.

Table 18

Lead Intake and Output of Normal Subject (M.R.) During Oral Lead Administration

Successive Periods of 12 Weeks	Lead Ingested Milligrams	Lead Eliminated—Milligrams			Lead—Mg. Lost (−) or Retained (+)
		Total	In Feces	In Urine	
1st	112·81	101·48	98·32	3·16	+11·33
2nd	118·74	108·95	103·74	5·21	+ 9·29
3rd	107·22	105·51	100·15	5·36	+ 1·71
4th	118·79	111·57	105·57	6·00	+ 7·22
5th	110·18	111·22	104·66	6·56	− 1·04
6th	116·22	121·59	114·15	7·44	− 5·37
7th	109·44	93·41	86·57	6·81	+16·03
8th	125·45	118·86	112·47	6·39	+ 6·59
9th	117·11	114·81	108·97	5·84	+ 2·30
10th	105·48	98·86	91·22	7·64	+ 6·62
11th	107·57	109·19	102·25	6·94	− 1·62
12th	114·24	102·06	94·03	8·03	+12·18
13th	113·14	100·68	94·02	6·66	+12·46
TOTAL ...	1,476·42*	1,398·19	1,316·12	82·07	78·23

* Approximately 22.00 mgs. in drinking water, 372.32 mgs. in food and other beverages, and 1,082.10 mgs. administered in solution.

The corresponding results of a more prolonged period during which one milligram of lead was ingested daily (in addition to that contained in the diet), have been combined for successive periods of 12 weeks in Table 18. These data demonstrate more clearly than those in Table 17, the uneven but generally progressive increase in the urinary output of lead, and they establish the occurrence of an irregularly progressive increase in the deficit in the total output of lead, as compared with the total intake. Apparently, under these conditions, lead was accumulating in the body of the subject. It is apparent, however, that there were times in the course of this experiment when the output of lead from the body was very nearly equivalent to the intake; there were also three periods, as shown in Table 18, when the output was somewhat greater than the intake. We shall examine these irregularities a little later.

The facts with reference to the sources and quantities of ingested lead, the avenues and the extent of the output, and the magnitude of the deficit referred to above, during the entire period of the experimental administration of lead, are summarized in Table 19. It may be noted here, for what it may be worth later, that the quantity of lead excreted in the urine during this period was practically equivalent to that retained in the body of the subject. A rough calculation will serve to show that approximately 70 milligrams of lead were excreted in the urine during the period of

Table 19
Lead Intake and Output of Normal Subject (M.R.) During Four-Year Period of Oral Administration of Lead

	Milligrams	Per cent of Total Ingestion
Ingested:		
In drinking water	30·00	1·5
In food and beverages	498·47	25·3
Administered in solution ...	1,442·80	73·2
TOTAL	1,971·27	100·0
Eliminated:		
In feces	1,739·31	88·2
In urine	113·77	5·8
TOTAL	1,853·08	94·0
Retained	110·07	7·8

abnormal absorption more than would have been excreted under normal conditions. This calculation is made by multiplying the gross urinary volume during this period, by the mean concentration of lead in the urine of this subject before lead was administered, and subtracting this product from the total output of lead in the urine. Disregarding the indeterminable quantity that may have occurred in the feces as a true excretion, which may have been of about the same magnitude as that excreted in the urine, this quantity (70 mg.), when added to that retained in the tissues, adds up to 180 milligrams that may credibly be taken to have been the minimum quantity of lead actually absorbed from the alimentary tract in the course of this experiment, roughly 13 per cent of that administered, or somewhat less than 10 per cent of the total quantity ingested.

At this point in the description of this experiment, it might serve the purposes of brevity and, at the same time, contribute information for comparison, if we were to introduce data corresponding to those of Table 19, but derived from another experiment, in which subject E.B. ingested two milligrams of lead per day, in addition to that in his diet, over the period of somewhat less than two years (684 days). This experiment was carried out in precisely the same manner as that of the first experiment and in concurrence with the latter part of it. The corresponding data are summarized in Table 20, in which it can be seen that approximately twice the daily dose of lead per day resulted in the accumulation

Table 20
Lead Intake and Output of Normal Subject (E.B.)
During Two-Year Period of Oral Administration of Lead

	Milligrams	Per cent of Total Ingestion
Ingested:		
In drinking water	12·00	0·8
In food and beverages	120·48	8·5
Administered in solution	1,286·85	90·7
TOTAL	1,419·33	100·0
Eliminated:		
In feces	1,236·19	87·1
In urine	73·07	5·1
TOTAL	1,309·28	92·2
Retained	110·07	7·8

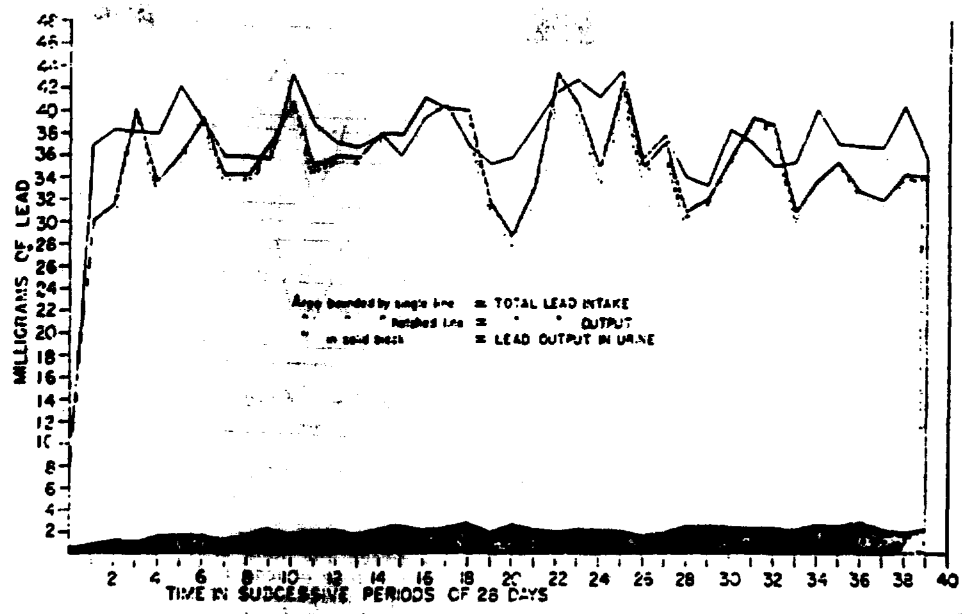

Fig. 1. Graphic representation of the quantities of lead taken in food, beverages and in solution with meals in each of 39 successive periods of 28 days, and the quantities eliminated in the urine and feces (combined) in the corresponding periods. Subject M.R.

of approximately the same quantity of lead in the body of subject E.B. in half the time. Again, the quantity excreted in the urine during the administration of lead was approximately the same as that retained in the body of the subject. The quantity of lead absorbed during the period of the administration of lead, arrived at by the same procedure as that indicated in the case of subject M.R. above, was certainly not less than 165 milligrams, which is about 13 per cent of that administered, and almost 12 per cent of the total quantity ingested. (The total quantity absorbed may well have been of the order of 200 milligrams, or 15 and 14.5 per cent, respectively, of the administered lead, and the total quantity of ingested lead.)

A graphic view of the gross quantitative relationships between the ingested lead (food, beverages, and that administered), that in the feces, and that in the urine, during 39 of the 52 periods (each of 28 days) over which lead was administered to subject M.R., is shown in Figure 1. Certain trends are clearly visible—the general course of the increase in the urinary output of lead, the essentially parallel variability of the total intake and output of lead during the total period portrayed, and the comparative constancy and yet the slightness of the discrepancy between the intake and output, as referred to previously in Table 19.

A further series of charts have been drawn up to reveal certain simple but significant facts. Thus in Figure 2, the output of lead in the feces may be seen to have a well-defined relationship to the lead ingested (since the amount administered was the same each day, the variability here derives from that of the food); it also bore a direct relationship to the regularity of the emptying of the alimentary tract. (In assembling the analytical results on the lead in the food and feces, for scanning as they were obtained, it could be noted that the failure of the subject to defecate during any 24-hour period resulted in a discrepancy between intake and output which was never fully counteracted subsequently; evidently, a greater degree of absorption of lead occurred when the retention of the contents of the alimentary tract was prolonged. In this manner, this factor came to light.)

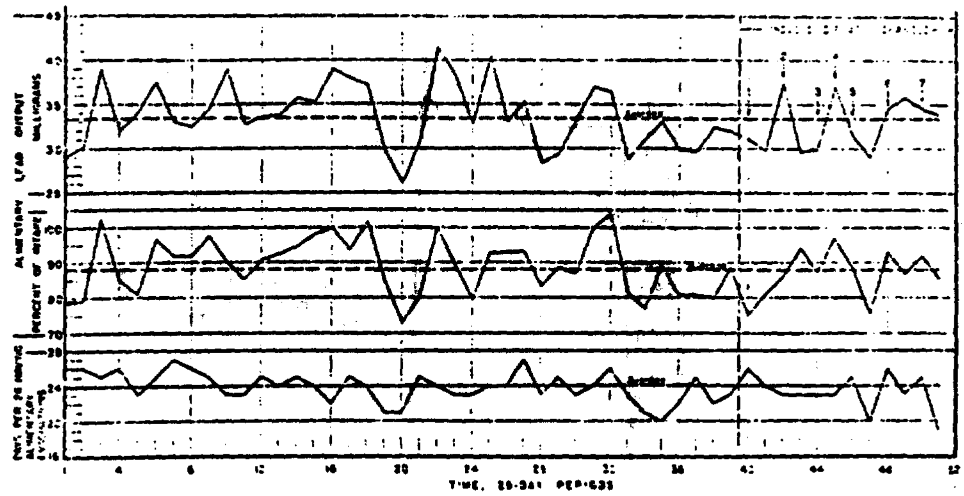

Fig. 2. The relation between the total lead output in the feces (uppermost series of connected points), the total intake of lead in food, beverages and in solution (middle series of connected points), and the irregularity (lag) of the fecal evacuations (lowermost series), as represented for each of 51 periods of 25 days, during a prolonged period in which 1 milligram of lead was ingested (with meals) daily. Subject M.R.

Certain facts with respect to the lead content of the urine and blood during the entire period in which lead was administered, are shown in Figure 3. The mean daily output of lead in the urine, the mean daily concentration of lead in the urine, and the average concentration of lead in the blood, for each 28-day period, are plotted. A point of outstanding importance is the general upward slope of the three curves. There are frequent peaks and valleys in each of them, as well as certain less frequent downward swings in the two representations of the urinary lead (which will be remarked upon later), but despite the frequent or infrequent recessions their eventual course mounts to progressively higher values. There is no evidence of the achievement of an equilibrium with the experimental conditions.

A further point of importance is the somewhat lesser rate of increase (more gradual slope of curve) in the concentration in the blood, as compared with that in the urine. This difference is not as evident at a glance, as it is when the sharp and frequent deviations of the curves are ironed out in fitted (straight line) curves, as illustrated in the case of the urine in Figure 4 below. (The lag on the part of the blood is the more pronounced, the higher the rate of absorption from the alimentary tract, i.e., the larger the dose of soluble lead ingested daily.) This phenomenon would seem not to be especially remarkable when one reckons with the fact that the concentration of lead in the blood of the normal individual is approximately 10 times that in the urine. Indeed its unusual feature is not that this discrepancy occurs but that it is not considerably greater, for such would certainly be the case but for the capacity of the erythrocytes to take up lead and thus retard somewhat its passage from the blood stream into both the tissues and the urine. As we shall see later, the usual limitation of the rate of the urinary excretion of lead does not depend on a normal incapacity of the renal apparatus to excrete lead beyond a certain low level, but upon the limited availability of lead for excretion. Thus when a sufficient quantity of lead is available in the body, the urinary excretion of lead may be augmented thirty-

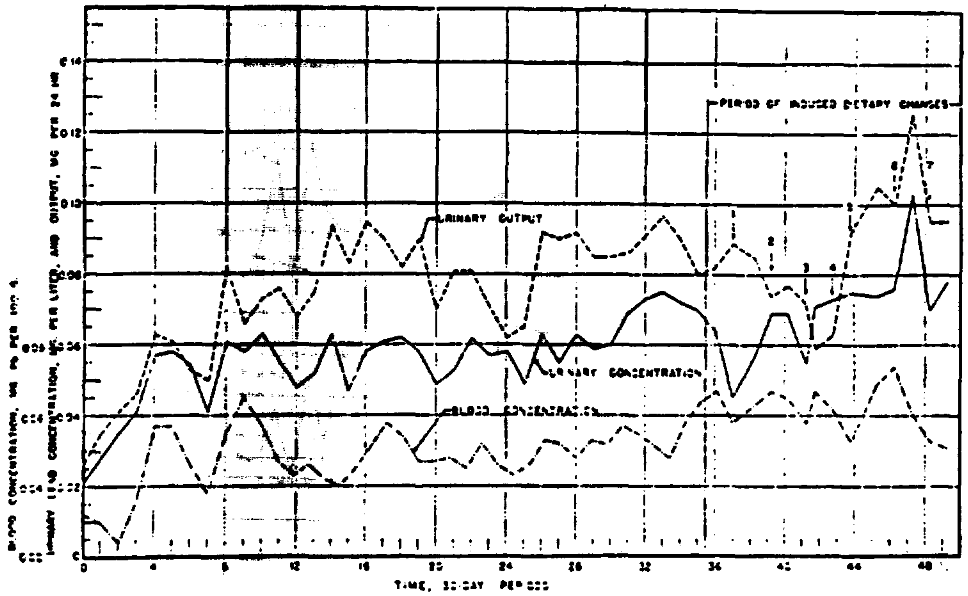

Fig. 3. Mean daily output of lead in urine, and mean daily concentration of lead in urine and blood, in each period of 28 days, during a prolonged period in which 1 milligram of lead, in solution, was ingested, daily, with meals. Subject M.R.

fold or even more. At such a time the concentration in the blood is likely to be increased only eight or tenfold. On the other hand, under circumstances associated with abnormal absorption of lead, and also with an impairment of the renal excretion of lead—a situation which occurs only rarely—the concentration of lead in the blood may be elevated by as much as twentyfold.

In Figure 4, the total output of lead in the urine, and the total volume of the urine, for each 28-day segment of the total period involved in the experimental administration of lead, are plotted in parallel. By this means, one is enabled to see that the volume of the urine is an important factor in the urinary output of lead, and also that (in Cincinnati) there is a well-defined seasonal factor which influences the output of water and the output of lead in an essentially parallel manner. Many (but not all) of the minor irregularities in the output of lead over the entire experimental period appear to be explainable on this basis, while the low points separated from each other by larger, serrated, upward loops, coincide with the peaks of summer heat, approximately a year apart. And yet, despite all of these deflections, the main course of the curve is steadily upward. Whether this curve is best fitted by a straight line may be questioned, but such a question at this point in our discussion may be dismissed as of little importance. The important point is the fact that there is no evidence here to suggest that the upward trend will diminish with further time. For aught one may suspect to the contrary, this same course might have continued upward through the remaining lifetime of the individual, so long as the experimental conditions were maintained, and, as we shall see later, this, in all likelihood, would have resulted disastrously for this experimental subject in somewhat more than three additional years. [The special experimental conditions represented in the latter part of the curves by the arrows under the heading "induced dietary changes," will not be dealt with here beyond the brief comment that they represent a series of crucial tests

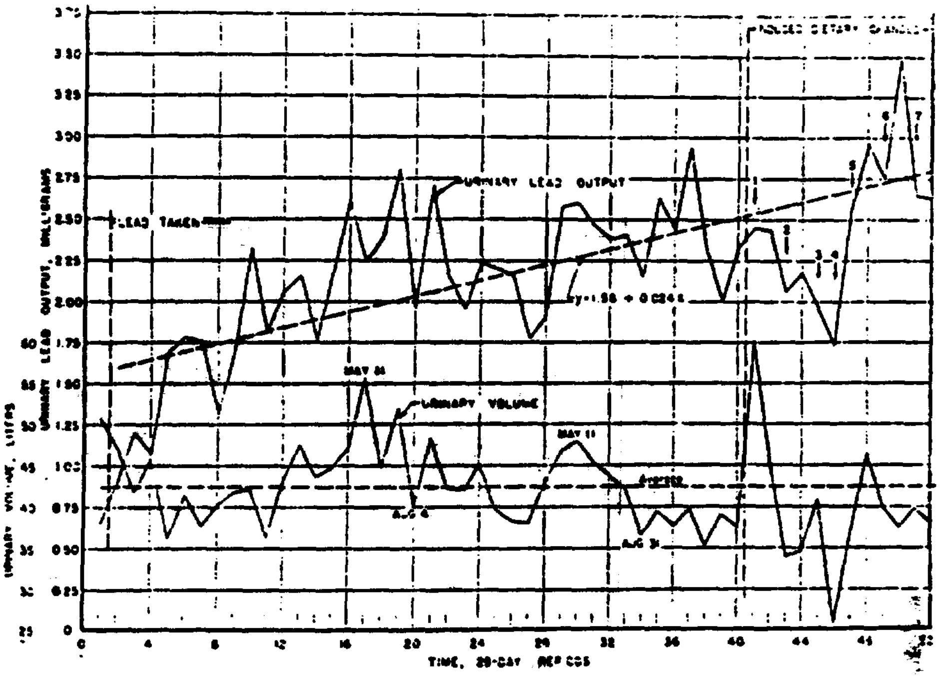

Fig. 4. The relation between the gross output of lead in urine and the gross volume of the urine, in successive periods of 28 days, during a prolonged period in which 1 milligram of lead, in solution, was ingested daily, with meals. Subject M.R.

of certain dietary or therapeutic methods of altering the retention of lead in the body, which can be seen to have influenced the output (and intake) of water, and thus only indirectly and insignificantly, the output of lead. These were, in sequence, (a) the administration of milk in large volume, (b) the administration of large doses of ascorbic acid, (c) deprivation of dietary calcium, (d) the deprivation of both dietary calcium and phosphate, and (e) the administration of excess of phosphate, and (g) the administra- excess of calcium, (f) the administration of tion of excess of calcium and phosphate, one administered in the morning, the other in the evening, to diminish their direct interaction. Each of these procedures was continued for 28 days, after which the subject resumed his usual regimen for 28 days, with the exception of procedures (c) and (d), the latter of which followed immediately in the wake of the former.]

In view of the apparent physiological and practical importance of the influence of the urinary volume upon the output of lead from the body, and in recognition of the dearth of quantitative information, derived from controlled conditions of experimentation, on this matter, the opportunity to carry out certain detailed observations of this type, in the course of this experiment, was too tempting to pass by. Since also there was little or no information as to diurnal variations in the concentration of lead in the blood, under fairly constant but abnormal conditions with respect to the absorption of lead, the blood and the urine of subject M.R. were sampled at intervals of two hours throughout a period of 24 hours on each of three different occasions during the period of administration of lead. The first observations were made five and one-half months after the initiation of the experimental ingestion of lead, the second, 19 months later, and the third, 10 months after the second. No additional experimental variable was introduced into the first series of observations, but in order still further to intensify the variability of the throughput of water, the second and third sets of observations were carried out as urinary dilution-concentration tests, the subject first being given an excess of water at the start of the observations, and then being deprived of water until the regimen of sampling had been completed. The results are plotted in Figure 5.

It will be noted that the concentration of lead in the blood varied only insignificantly (only one result, on 9th January, 1940, ranged above the upper limit of analytical variability) during any one of the 24-hour periods, but that the level of concentration increased step by step in the

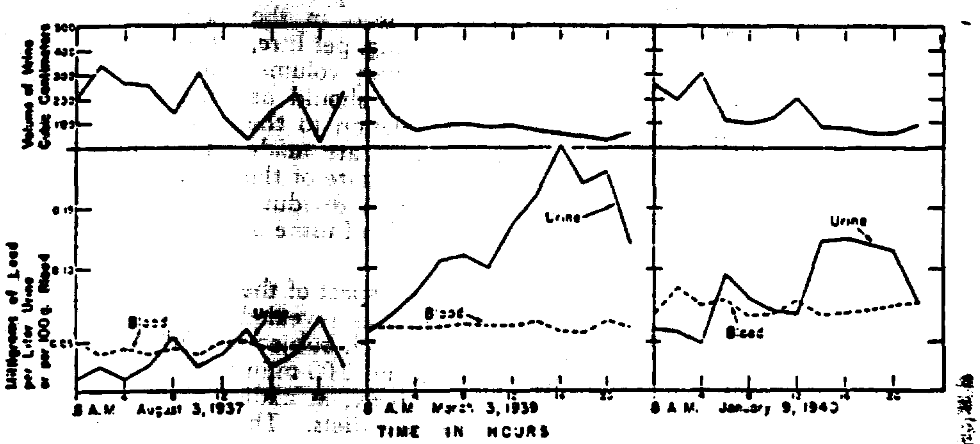

Fig. 5. Diurnal variations in the concentration of lead in the urine and blood (lower sections), in relation to normal (left, upper section) and induced (centre and right upper sections) variations in the volume of the urine, during three 24-hour periods in the course of a prolonged period of experimental ingestion of lead. Subject M.R.

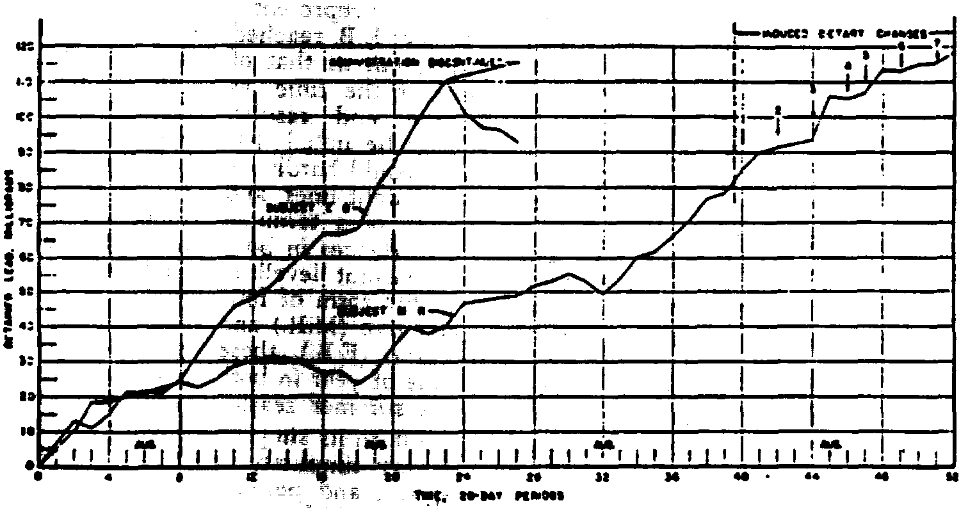

Fig. 6. The cumulative difference between the gross intake of lead in food, beverages and that ingested in solution, and the gross output in the feces and urine, in successive periods of 28 days, during prolonged periods of experimental ingestion of lead. Subject M.R. (1 mg. per day in solution) and subject E.B. (2 mg. per day in solution). Each point represents the total quantity of lead retained in the body of one of the subjects at the corresponding period of the experimental sequence.

successive periods. The urinary concentration of lead, on the contrary, varied widely within each period, in inverse relation to the urinary volume. The extreme expression of this variability occurred when, on the same day (3rd March, 1939), while the concentration of lead in the blood remained essentially constant at 0.053 mg. per 100 grams, the concentration of lead in the urine ranged from 0.05 to 0.21 mg. per litre, at the opposite poles of the urinary volume. This high degree of variability should be noted and remembered in relation to the frequency with which attempts are made to establish the general level or rate of the current absorption of lead by an individual, through the analysis of a sample of urine of small volume.

Next in Figure 6, is another aspect of the abnormal metabolism of lead, as revealed in the two experiments in which subjects M.R. and E.B. ingested 1.00 and 2.00 milligrams of lead daily, respectively, in addition to that in their respective diets. The cumulative retention of lead (the gross difference between intake and output in the bodies of these subjects) is plotted on a month by month (28 day) basis, the resultant two curves being practically the same except for their slopes and their representation in time. That is, subject E.B. reached practically the same end-point as that of subject M.R. in about half the time, as shown previously in the end results, Tables 19 and 20. It may be noted that the points on these curves could hardly be fitted by any other than straight lines, and that there is no suggestion of a terminal levelling off. There are evidences in both curves, however, of a recurrent levelling and downward trend, in the form of four notches in the four-year curve (M.R.) and two in the two-year curve (E.B.), these occurring at the same time of year in both instances, namely, in the summer season.

The meaning of Figure 6, in its simplest terms, is clear, but the very simplicity of the facts may be deceptive, and perhaps some further consideration should be given to them. These two experimental subjects, as well as a third (subject I.F.) who ingested three milligrams of lead, as a dissolved salt, every day for four months, suffered no deviation from a state of well-being during these experiments, and, therefore, it might be concluded that these daily dosages of lead have been proved, thereby, to be harmless. So they were, for the period of time represented in the experiments. If, however, there is a point at which the accumulation of lead in the body becomes, of itself, dangerous (evidence will appear, subsequently, to show that this is the case), we must view these experiments in a different light. Unless these subjects, if continued indefinitely under their respective conditions of lead intake, should, at some time, achieve an equilibrium whereby the intake and output of lead would come into balance, they might well be threatened with lead intoxication at some time. It is important to recognize, therefore, that no evidence of an approach to such an equilibrium is offered by the results of these experiments. We shall return to this matter at a later and more appropriate point.

As to the seasonal variation in the lead metabolism of subjects M.R. and E.B., no satisfactory interpretation can be given. It is pertinent, however, to call attention to the fact that the excretion of lead in the sweat of these subjects, to whatever extent it may have occurred, is not accounted for in these curves or in any other representations of our data. If such data were available for inclusion, they would further increase the loss of lead from the body, and would increase the negative metabolic balance, thus deepening the notches in the curves of Figure 6. It is evident, then, that there was a greater excretion or a lesser absorption of lead by these subjects in the summertime, but the reason for this phenomenon is a matter for speculation. Was it temperature *per se*, or sunshine, or the greater seasonal recreational exertion of young persons, or the greater use of fresh vegetables and fruit during the summer months, or was it some more subtle change in the general metabolism of the body?

A further experimental variable, that of dosage, remains to be examined for its comparative effects upon the patterns of response of the several subjects. These effects can be illustrated in a few charts and comprehended promptly and with little further explanation. It may be of interest to mention the fact that the dosage of 0.3 mg. of lead per day, taken by subject S.W. (in addition to that in his diet), was selected by means of a rough calculation, in the belief that it might result in an amount of alimentary absorption equivalent to that being absorbed in the respiratory tract. This subject had just completed a period of 13 lunar months of observation under normal (control) conditions, during which his output in the feces and urine had exceeded his intake in food and beverages by 8.58 milligrams. This excess was regarded as having been absorbed from the atmosphere in the respiratory tract. If our estimate of the appropriate dosage for use in this experiment had turned out to be correct, the intake and output of lead, charted in the usual manner, would have been in balance, and the actual amount of the respiratory absorption would have been indicated by this indirect procedure. This turned out not to be the case, but it eventuated that this was the least dose which, when ingested, would be absorbed to such an extent as to yield incontrovertible evidence thereof within a few months. This fact and certain others are shown in a series of charts.

Figure 7 portrays the mean daily alimentary intake and output of lead by subject S.W., during the 11.5 lunar months of the control period, and for the 17 months thereafter, during 15 of which, the dose of 0.3 mg. of lead was ingested daily. This chart is introduced merely to demonstrate again, for emphasis, the familiar relationship of the alimentary output of lead to the alimentary intake, over the entire period of the observations. The extent and the abruptness of the changes associated with the initiation and the termination of the period of experimental ingestion of lead are apparent.

The situation is different, however, when evidence is sought of the absorption of lead from the alimentary tract, under the conditions of this experiment, by examining the data as they are set down graphically in Tables 8 and 9. The two lowermost curves of Figure 8 represent the mean quantities of lead excreted per day in the urine by subject S.W. during each 28-day period of this entire experiment (the period of ingestion being superimposed, for purposes of comparison, upon the control period). In three of the periods of 28 days during the experimental ingestion of lead,

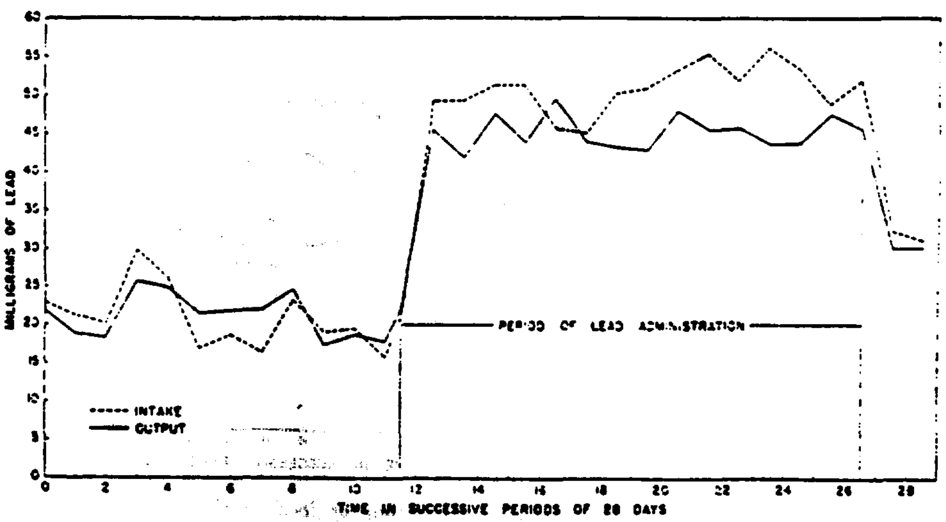

Fig. 7. The gross intake of lead in food and beverages and the gross output of lead in the feces, for each period of 28 days in sequence, are plotted as indicated, in the initial and final sections. The lead taken in solution along with the food, is added to that in the food, in each successive period of 28 days, during the total period in which 0.3 mg. of lead was ingested daily. Subject S.W.

the output of lead in the urine was significantly greater than it had been in the corresponding part of the control period, and, during the latter part of the period of ingestion, the general trend of the urinary output of lead appeared more and more to deviate from strictly normal levels. Most of the time, however, during the period of ingestion, the difference between the two curves may be seen to have been negligible. The over-all difference is barely of statistical significance. The other curves in Figure 8, with the exception of that of subject I.F. (3 mg. of lead per day), whose period of ingestion was too brief to bring out the main or ultimate slope of this curve, reveal their own trends and diverge from each other and from the baseline in a generally definitive manner. These elongated curves are plotted on approximately the same seasonal basis, and although there is some degree of conflict in their seasonal trends, simple inspection is a sufficient means of differentiating them in relation to the daily dosage of ingested lead.

Figure 9 provides a comparison of curves which differ in their construction from those in Figure 8, only in that each point represents the mean concentration, instead of the mean quantity, of lead in a series of 28 samples of urine each of which was one day's output, these being plotted in temporal sequence. The visual comparisons are facilitated by the inclusion of a straight line representing a mathematically derived slope for each curve (except that representing the control period of subject S.W.). There was a barely significant increase in the concentration of lead in the urine of subject S.W. during the period of ingestion. The other curves bear much the same relation to each other as those in Figure 8. In Figure 9, however, the inadequacy of the curve (subject I.F.) which is intended to represent the response to the

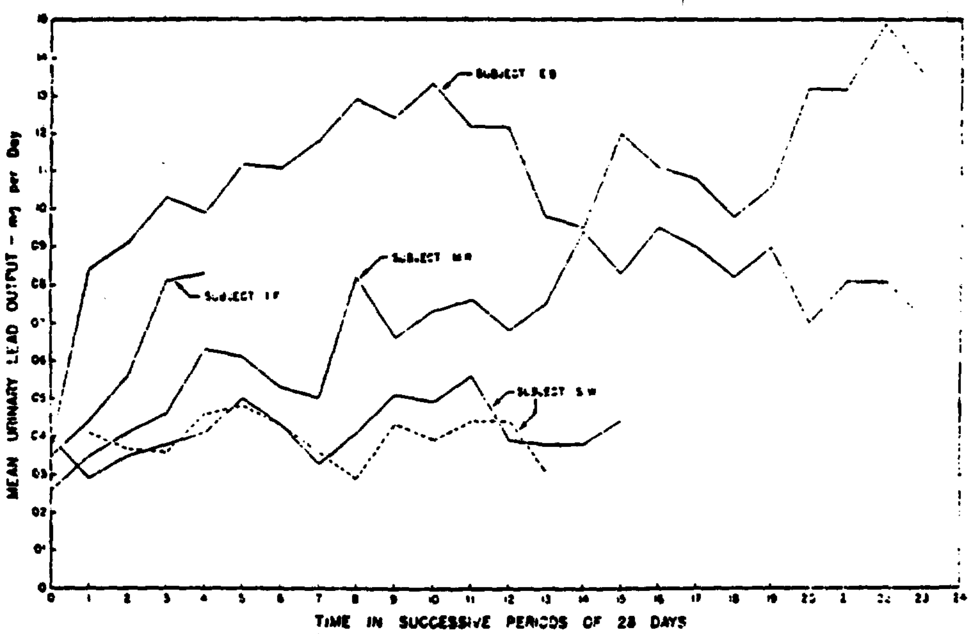

Fig. 8. The mean daily output of lead in the urine of each subject as identified, in successive periods of 28 days, including the preliminary (control or base-line) values of subjects M.R. (1 mg. per day), E.B. (2 mg. per day), and I.F. (3 mg. per day). Subject S.W. is represented by two curves, one broken, portraying the period during which no lead was taken with meals, and the other, continuous, covering the period during which he ingested 0.3 mg. of lead per day. The points plotted in the case of subject M.R. represent only the first 23 of 52 periods, which could be compared with those of subject E.B.

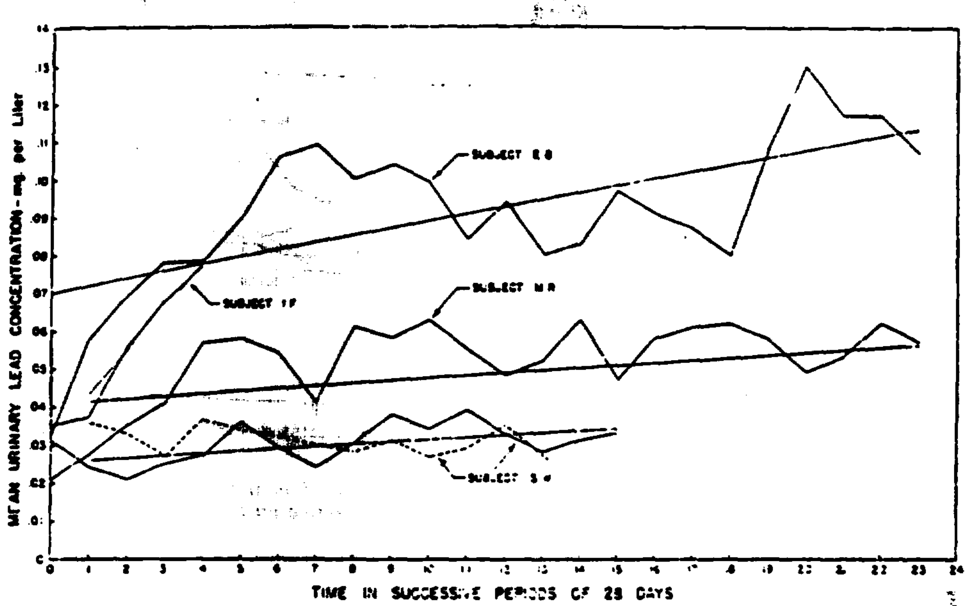

Fig. 9. The mean daily concentration of lead in the urine of subjects S.W., M.R., E.B., and I.F., plotted for comparative purposes in exact accordance with the arrangement in Figure 8.

ingestion of 3 mg. of lead per day (plus that in the food), seems evident, for while the two adjacent and more prolonged curves tend to level off somewhat after an initial sharp rise, this one, seemingly, portrays only the initial slope. One would like to know what would have been its future course had the experiment been prolonged.

The occurrence or nonoccurrence of significant changes in the concentration of lead in the blood of the four subjects during these experiments is shown graphically in the curves of Figure 10. The two which represent the two periods of the experiment involving subject S.W. cannot be differentiated, nor could these two sets of data be differentiated by statistical means. It is possible that these curves would have diverged significantly, if this subject had adhered to the same experimental regimen for a longer period of time. This is not certain, however, and the fact is clear that the absorption of lead at this level of oral dosage is so minute as to be barely demonstrated only by a slight increase in the rate of the urinary excretion of lead, without the confirming evidence of an increase in the concentration of lead in the blood.

The curves which show increases in the concentration of lead in the blood, in association with varying rates of absorption of lead, slope much more gently upward from the base line than do those indicative of the rates of the urinary excretion of lead (Fig. 9), and they tend to differentiate themselves from each other to a lesser extent and more gradually than do the corresponding urinary slopes. On the other hand, it follows that every demonstrable change in the blood is more significant, in terms of the degree of absorption of lead which induced it, than is a comparable degree of change in the urinary output or concentration of lead.

A passing reference was made, at the beginning of this discussion of the metabolism of lead under abnormal conditions, to means of hastening the elimination of lead from the body—"deleading", as this has often been spoken of. The accomplishment of this purpose has been a persistent goal of medical therapy, and many remedies, among which were potassium iodide in an earlier period, ammonium

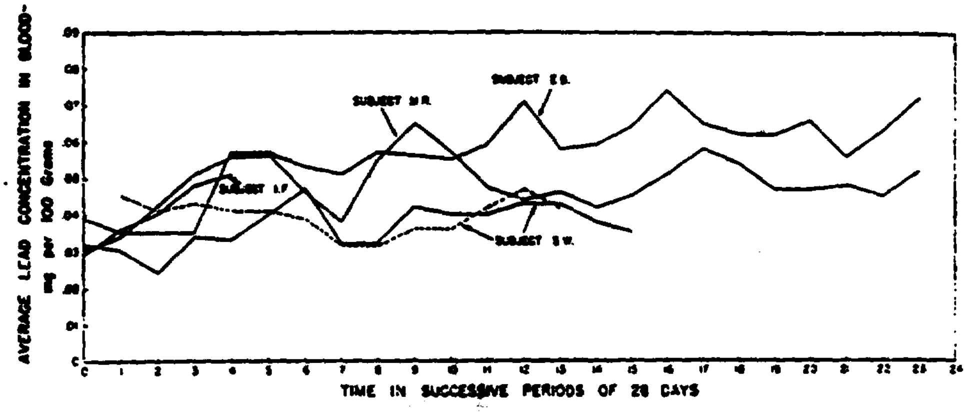

Fig. 10. The mean concentration of lead in the blood of subjects S.W., M.R., E.B., and I.F., plotted for comparative purposes, as in Figures 8 and 9.

chloride more recently for a time, and sodium citrate still more recently and on different theoretical grounds. None of these agents is of any practical value in speeding the elimination of lead from the body. (Whether they may yield therapeutic benefit otherwise, is another matter.) An obstacle to the clarification of this and certain other questions of clinical and legal medicine, has been the almost utter lack of precise information concerning the manner and the proportional extent, and, more particularly, the rate and duration, of the elimination of lead from the body, following varying periods of abnormal absorption. Every physician has known, or considers that he knows, about the cumulative characteristics of lead, but few have concerned themselves to know anything definite about the eventual outcome of the ordinary processes of elimination. It is almost as though, in general medical belief, lead accumulates in the body in the absolute sense and without expectation of a reversal of the process, except through the intervention of therapy or intercurrent disease. It would be an astonishing physiological phenomenon if this were true, but, as has been known for some time, it is not. Some of the facts have been disclosed by prolonged observations of the rate and extent of the excretion of lead by patients or industrial employees who had terminated their occupational exposure to lead temporarily or permanently (10). The experiments described herein elucidate the matter still further, however, because of the completeness and the quantitative character of the information which they supply on all aspects of the matter.

In addition to the fact that, after the termination of a period of abnormal absorption, a variably prolonged period of elimination of the accumulated lead ensues —that is, an excess of output over intake— there is also a variation in the rate of this loss, from one individual to another, dependent upon, (a) the amount of lead which accumulated during the period of abnormal absorption, and also (b) upon the length of time involved in the accumulative process. These features of the elimination of absorbed and retained lead are illustrated, in part, in Figure 11, in which are represented graphically the cumulative retention of lead by each of this series of experimental subjects, during a period of daily experimental ingestion of a known quantity of lead, and the accumulative loss of lead during a period following the termination of the experimental ingestion of lead. Figure 11 also includes the graphic representation of the corresponding behaviour of two subjects who ingested only such lead as was contained in their food and beverages.

The legend of Figure 11 provides the additional information required to clarify certain of the details of the manner of representation employed, but some comment may be required to bring out the more important relationships. First, it should be noted that it contains a family of related and similar curves. The two subjects represented in the two lowermost and substantially identical curves, eliminated more lead in their urine and feces, which lead accumulated in the bodies of these subjects are indicated by the primary slopes of the respective curves, which varied directly with the quantities of lead ingested daily. The actual quantities accumulated varied correspondingly, being represented, in the intermediate and final periods, by the points on the curves. Despite the fact that two of the curves (those of subjects M.R. and E.B.) tended to coincide in their early courses (during the first 8 months of each), the metabolic behaviour of the individuals was clearly differentiated otherwise, according to dosage.

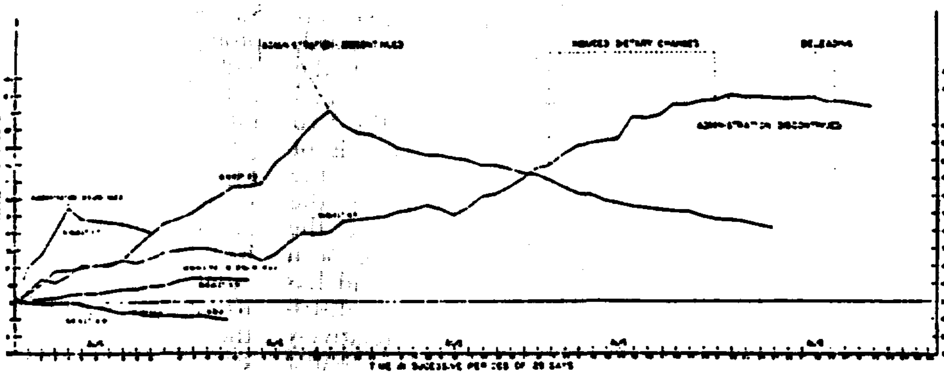

Fig. 11. The cumulative difference between the gross alimentary intake of lead, and the gross output of lead in the feces and urine, in successive periods of 28 days, over the periods of time indicated. The two lowermost curves represent the negative balance as observed in subjects S.W. and I.F., under normal (base-line) conditions. The upward slopes of the four above the base line represent, from below upward, the relative rates of accumulation, and the points give the quantities of lead accumulated by subjects S.W., M.R., E.B. and I.F., during the periods indicated, in which they ingested, in solution, daily 0.3, 1, 2, and 3 mg., respectively, of lead. The downward slopes of the three curves identified as pertaining to subjects I.F., E.B., and M.R., represent the rates of the progressive losses of lead, following the termination of the respective periods of experimental ingestion of lead, while the points indicate the quantities of absorbed and accumulated lead remaining within the bodies of the respective subjects.

month by month, than they ingested with their food and beverages. As indicated in the first lecture, this is readily explained by the lack of any representation in the analytical data of the lead inhaled and absorbed from the atmosphere. The other curves, which, from below upward, represent the behaviour of subjects S.W., M.R., E.B., and I.F., who, in addition to the lead in their diets, ingested 0.3, 1, 2 and 3 mg. of lead per day, respectively, show that each of these subjects ingested more lead than he eliminated. The relative rates at

When the intake and output of lead of the three subjects were followed after the termination of the experimental ingestion of lead, the situation was reversed and the lead that had been accumulating now diminished. The eliminative process, in each instance (after a brief period of relatively rapid decrease in two of the three), proceeded at rates which were appreciably lower than the respective rates of accumulation, and appeared to vary inversely, among the three, with the length of time over which the accumulation had occurred. The different rates at which the previously accumulated lead was eliminated are illustrated most strikingly by the prolonged observations on subjects M.R. and E.B., and the difference between these two subjects was especially pronounced, despite the fact that the total quantities of lead which they had retained (the one in four years, and the other in two) were very nearly identical. If it be assumed that the metabolic reactions of the two subjects were much the same, the conclusion is almost inescapable that the respective rates of elimination depended upon some factor associated with the length of time required to accumulate a given quantity of lead in the two instances. Such a factor may be visualized, in contemplating the evidence that the large proportion of the retained lead had gone into the osseous tissues of the two subjects, in which, in the two periods of time, disproportionate quantities of the retained lead had found their way into the more sluggishly metabolizing regions of the respective bony structures. It has been observed at necropsy, that when lead has been absorbed rapidly, it is unevenly distributed in a bone, being found in relatively high concentration in the more vascular and more rapidly metabolizing areas; but when lead is absorbed very slowly, or at a low level intermittently, or when a long period of time has elapsed since the occurrence of abnormal absorption, the concentration of lead in all parts of the bone tends to be more nearly uniform (11). It may be noted, in this relationship, that under normal conditions, lead is found in higher concentrations in the relatively avascular long bones of the skeleton than in the flat (Table 16, Lecture 1), whereas the opposite relationship obtains in fatal cases of lead poisoning (Table 27, Lecture III).

It is of interest to examine Figure 11 further, from the aspect of the absolute length of time that may be required for the elimination of a given quantity of lead retained in the body during a period of abnormal absorption. This obviously is related directly to the foregoing discussion of the rates of elimination, but from the practical viewpoint, it is important to think in definite temporal terms. It may be observed that subject M.R. eliminated very little of his retained lead during the period of 10 months (actually only 7 to 10 milligrams). This was due in part to the unfortunate circumstance that, with the termination of the period of experimental ingestion, this subject altered his mode of living somewhat, and, as is likely to happen at such times, the quantity of lead in his diet changed. In this instance it was increased appreciably for approximately two months. Despite this experimental variable, however, it was evident that the elimination of the lead which he had retained during the experiment would require a long time. Subject E.B., on the other hand, began promptly to eliminate the lead which he had retained, and he continued to do so at a fairly steady but gradually diminishing rate, for about 30 months, after an initial period of about two months of relatively rapid loss. During the total period (32 lunar months, 896 days) he eliminated approximately 79 of the 110 milligrams he had accumulated in his body in 23 lunar months (half of the retained lead had been eliminated in 23 lunar months). Neither of the other subjects was followed long enough (the importance of doing so was not evident at the time, and it would have been difficult to do so in either case to provide results which can now be compared with those obtained in the case of subject E.B. There is good reason, from the trends of the other two curves, and in view of the comparability of the other aspects of their metabolic patterns, to infer that subject I.F. reduced his retained lead by half in something more or less than eight months, while subject M.R. could hardly have reached a similar state (that of half of his experimentally induced "body burden") in much less than five years. These are, of course, rough estimates, but they provide some support for a "rule of thumb," which in the case of subject E.B. is based on reasonably firm ground. One may state such a rule in his case, and may perhaps apply it, with some reservation, to other situations involving approximately two years of abnormal absorption to the effect that about twice the length of time was required to eliminate the accumulated lead, as that involved in its accumulation. The other subjects fall on one side or the other of this estimate, as will also those individuals whose abnormal absorption of lead has resulted in accumulation over short or long periods of time.

Another incidental feature of Figure 11 is concerned with the lack of any visible effects in association with the "induced dietary changes" (which have been referred to previously) in the case of subject M.R., and with the correspondingly negative effect of the indicated attempt at "deleading." The latter, introduced into the experiment only after an interval of time sufficient to permit the normal eliminative processes to demonstrate their operation, but before there had been any *considerable diminution in the body burden* of lead, consisted in providing subject M.R. with a diet very low in calcium, and in the administration of ammonium chloride in increasing dosage up to the point of tolerance, over a period of six weeks. The effect, in terms of the elimination of lead during this period, was clearly negligible. It has been an accepted fact for some time that this type of eliminative regimen is ineffectual, and mention is made of it here only for the sake of a full representation of the details of this experiment. This experimental procedure was not without point at the time it was undertaken.

In the conduct of the group of experiments concerned with the ingestion of lead, opportunities presented themselves for seeking answers to a number of questions that are of interest to physiologists and also to clinicians. Only a few of such questions were pursued in a manner that required a departure from a simple and ordinary routine of performance on the part of the subjects. The data, on the other hand, have been examined by various means and in various relationships in search of significant items of evidence. They will be returned to again and again, no doubt, as further questions arise. One such procedure was that of examining the data obtained during the period following the termination of the experimental ingestion of lead. This period, when lead was being excreted in greater quantities than those being absorbed, was especially favourable for the determination of the relationship between the urinary and the true alimentary excretion.

Tables 21 and 22 display the observed facts, as well as the calculations and the assumptions, on which are based the estimation of the urinary and the alimentary excretion of lead by subjects M.R. and E.B. respectively, during the terminal periods of these two experiments. The steps in the calculations were those of (1) summing up the excess of the output of lead of each subject over the intake, follow-

Table 21

Lead Intake and Output of Normal Subject (M.R.) during the Period of 280 Days after the Termination of the Oral Administration of Lead

Ingested lead :		
In food and beverages		92·18 mgs.
Eliminated lead :		
In urine	15·99 mgs.	
In feces	83·43 mgs.	
TOTAL		99·42 mgs.
Excess of Elimination		7·24 mgs.
Excess excreted in urine	10·11 mgs.*	
Excess excreted by alimentary tract	—2·87 mgs.	
TOTAL		7·24 mgs.

* Arrived at by calculating what would have been the normal urinary output for this period, by multiplying the total volume of the urine during this period by the mean normal concentration of lead in the urine of this subject, and subtracting this product from the total amount of lead eliminated in the urine during this period.

ing the termination of the period of abnormal absorption, for a period of time sufficient, presumably, to cancel out the errors of sampling of the food and feces; (2) of calculating what would have been the normal output of lead in the urine during this period, and subtracting this amount *from* the actual output during the period (the normal output was taken to be the product of the total volume of the urine in litres, *during* this *period*, multiplied by the mean normal concentration of lead in the urine of the subject as originally determined, expressed in the proper decimal of a milligram per litre); and (3) of subtracting the value in (2), which will represent the excess of lead excreted in the urine. from the total excess, and regarding this difference as the excess of lead actually *excreted* via the alimentary tract. This method is not strictly precise, but it is correct in principle, and can be expected to yield results that err only slightly, and are certainly of the correct order of magnitude. According to Table 21, subject M.R., excreted a quantity of lead in his urine of the order of 7 to 10 mg. (dependent upon which value is accepted) in excess of that which was taken into his body and negligible, in view of the evidence to which attention was called previously, that a normal subject may eliminate approximately 6 mg. of lead (8 mg per year) during such a period as this. The elevation of the output and the concentration of lead in the urine after the termination of the abnormal absorption provides adequate evidence, however, of the excretion of previously absorbed lead in the urine. The quantity of lead so excreted in excess of that normally excreted, is more nearly correct, in all probability, than is the quantity indicated by the gross difference between intake and output, for the reason that, under the conditions of these experiments, errors in the sampling of the urine are less numerous and smaller than those associated with the duplication of the food consumed daily. We may reasonably take it. from these observations, therefore, that satisfactory evidence has been afforded in Table 21 of the excretion of the excess of lead via the urine. but that it has yielded no valid evidence that any of the retained lead was excreted by subject M.R. via the alimentary tract.

The evidence in Table 22 is different. Subject E.B., when considered in the same manner as subject M.R. eliminated approximately 40 milligrams of lead more than he took in during the period of 448 days of these observations. The same methods of calculation indicate that approximately equal amounts of the retained lead were excreted in the urine and feces.

Table 22

Lead Intake and Output of Normal Subject (E.B.) during the Period of 448 Days after the Termination of the Oral Administration of Lead

Ingested lead :		
In food and beverages		148·20 mgs.
Eliminated lead :		
In urine	35·61 mgs.	
In feces	153·04 mgs.	
TOTAL		188·65 mgs.
Excess of Elimination		40·45 mgs.
Excess excreted in urine	19·13 mgs.*	
Excess excreted by alimentary tract	21·32 mgs.	
TOTAL		40·45 mgs.

* Arrived at in the same manner as the corresponding value in Table 21.

absorbed during the period of 280 days with which we are concerned in this relationship; during this same period he did not excrete any of the retained lead by way of the alimentary tract. The actual excess of the gross output of lead over the gross intake during this period was almost

The meaning of these somewhat disparate results in the two instances is not entirely certain. It seems improbable that there was any great difference in the operation of the basic metabolic mechanisms of these two subjects. Rather, it is probable that the principal difference in their excretory behaviour during these corresponding experimental periods lay in the difference in the quantities of lead in active transit in the two instances. We have observed that, when the quantities of lead being excreted by certain patients were quite large, in the absence of continuing respiratory exposure to particulate lead compounds, the alimentary lead appeared to be appreciably greater than that which could be accounted for by the lead ingested in food and beverages. It seems likely, therefore, that the alimentary excretion of lead begins to contribute to the total excretory process, when the lead in transit reaches a suitable threshold, and that it contributes proportionally more, as the quantity of lead in transit increases. We have observed persons whose true alimentary excretion of lead appeared to be three or four times that in the urine (in the absence of renal impairment), and we have also seen others, as in the case of subject M.R., whose alimentary excretion of lead appeared to be negligible. There is no doubt, of course, that lead is excreted in the bile, but at its point of discharge into the alimentary tract it has a long way to go and a long time in which to be absorbed before being evacuated.